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Early norepinephrine for patients with septic shock: an updated systematic review and meta-analysis with trial sequential analysis

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Abstract

Background The optimal timing for initiating norepinephrine in septic shock is debated. This updated systematic review and meta-analysis aimed to evaluate the impact of early versus delayed norepinephrine initiation on mortality and clinical outcomes in adults with septic shock.

Methods A systematic search in Pubmed, EMbase and the Cochrane Library to identify eligible randomized controlled trials, propensity score matching (PSM) and observational studies that compare early norepinephrine initiation with non-early norepinephrine initiation in patients with acute circulatory failure. The primary outcome was mortality in intensive care unit. Secondary outcomes included intensive care unit length of stay, fluid volume received at 6 h, norepinephrine dose, mechanical ventilation-free days, renal replacement therapy free days, and time to achieve a targeted mean arterial pressure (MAP). Meta-analysis and subgroup analysis were conducted to calculate odds ratio (OR) or mean difference with 95% confidence interval (95%CI) using random-effect model. Trial sequential analysis was conducted to evaluate the conclusiveness of evidence.

Results Ten studies (two RCT, three PSM and five observational studies) involving 4767 patients were included. Early norepinephrine significantly reduced mortality in RCT (OR 0.49, 95%CI 0.25–0.96; $I^2=45\%$, $p=0.04$), pooled RCT and PSM (OR 0.65, 95%CI 0.42–0.99; $I^2=74\%$, $p=0.05$), and observational studies (OR 0.71, 95%CI 0.54–0.94; $I^2=66\%$). The trial sequential analysis indicated more data are needed. Subgroup analyses showed reduced mortality with early norepinephrine when lactate was ≤ 3mmol/L and administered within 1 h. Secondary outcomes showed a reduced fluid volume at 6h (RCT + PSM: mean difference −502 mL, 95%CI −899 to −106; $I^2=91\%$, $p=0.01$), faster MAP target achievement (RCT + PSM: mean difference −1.30h, 95%CI −1.75 to −0.85; $I^2=0\%$, $p<0.01$), more mechanical ventilation-free days (RCT + PSM: mean difference 3.99 days, 95%CI 2.42–5.57; $I^2=32\%$, $p<0.01$) and smaller cumulative norepinephrine dose (Observational: mean difference −3.44 mcg/kg, 95%CI -6.13 to -0.76; $I^2=0\%$, p = 0.01) in the early initiation group compare to the non-early initiation group.

Conclusion Early norepinephrine introduction in septic shock is associated with reduced mortality, decreased fluid volume administered at 6 h, faster time to achieve MAP target and more mechanical ventilation-free days. However, the trial sequential analysis indicates that further RCT are still needed to confirm these findings.

Keywords Acute circulatory failure, Fluids, Hemodynamic, Timing, Vasopressor

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Introduction

Septic shock is the most common critical condition in intensive care units, consistently associated with high mortality rates [1]. Treatment is based on rapid correction of relative and sometimes absolute hypovolemia by fluid resuscitation. A vasopressor is added if the hemodynamic state is not corrected by correction of the hypovolemic component of acute corticosteroid insufficiency. Norepinephrine is a potent α-1 and β-1 adrenergic receptors agonist, which results in improved cardiac contractility [2], arterial and venous vasoconstriction [3, 4] and a rapid increase in mean arterial pressure (MAP) [5]. Norepinephrine is the preferred first-line vasopressor agent [6].

However, the optimal timing for initiating vasopressor therapy during the resuscitative process remains a subject of debate. The Surviving Sepsis Campaign does not specifically address when norepinephrine should be started in relation to correcting the hypovolemic component of septic shock, although it is suggested that it be started early in cases of life-threatening hypotension [6]. Early administration of norepinephrine may restore arterial pressure more rapidly than fluid resuscitation alone, it may increase cardiac preload by recruiting some unstressed blood volume, and also recruit some cardiac contractility. Nevertheless, starting norepinephrine before the hypovolemic part of septic shock has been corrected may induce excessive vasoconstriction and induce tissue ischemia. Moreover, initiating norepinephrine earlier may increase the time of exposure to catecholamines and total dosage administered, the latter being possibly associated with poor prognosis [7].

To settle the debate, few studies only are currently available. Some of these have been previously reviewed and meta-analyzed in the journal [8], but some were more recently published [9–12]. Thus, we performed an updated systematic review and meta-analysis of studies investigating the timing of norepinephrine administration in patients with septic shock.

Methods

Protocol and registration

This study was prospectively registered with PROSPERO (CRD42023424058, June 16, 2023) and conducted in accordance with the PRISMA guidelines.

Literature search

PubMed, Embase, and the Cochrane Central Register of Controlled Trials from inception to September 2024 were systematically searched. The search strategy included keywords and medical subject heading terms for norepinephrine initiation time (Appendix 1). The reference of relevant reviews and included studies were also verified to search for additional eligible studies.

PICO statement

Studies were considered eligible if they met the following criteria: (i) design: randomized controlled trials (RCTs), propensity score matching (PSM) studies, and observational studies; (ii) population: adult patients with septic shock; (iii) intervention: early initiation of norepinephrine; (iv) comparison: non-early norepinephrine initiation; and (v) outcome: mortality. The criteria used for defining septic shock, timing of norepinephrine administration and mortality in the included studies are presented in Supplementary Table 1.

Study selection

Two reviewers (RS and RB) independently removed duplicates, screened the titles and abstracts for relevance, and assessed the full-text articles for inclusion based on the pre-specified eligibility criteria. In cases of disagreement, a third author (CL) provided a decisive opinion.

Data extraction

Two reviewers (RS and RB) independently extracted data using a standardized data extraction sheet including the following information: first author, year of publication, proportion of male, country where the study was conducted, age, number of patients, severity scores, time and modalities of norepinephrine administration and outcomes.

Outcomes

The primary outcome was mortality. A subgroup analysis for mortality was conducted based on lactate levels (≤ 3 mmol/L *vs.* >3 mmol/L) and timing of norepinephrine administration (≤ 1 h *vs.* >1 h). For subgroup analyses, we used the pre-randomization value of variables in RCTs, and values collected at baseline for PSM and observational studies. Secondary outcomes included intensive care unit length of stay (ICULOS), fluid volume received at 6 h, norepinephrine dose, mechanical ventilation free days, renal replacement therapy free days, and time to achieve a targeted mean arterial pressure. The definition of these outcomes was consistent with the original studies (Table 1).

Risk of bias and GRADE assessment

The risk of bias for each outcome in observational studies was assessed using the Newcastle–Ottawa Scale Tool, while the Cochrane Risk of Bias Tool (RoB 2) was employed for RCTs [13, 14]. Two authors (RS and RB)

Table 1 Design of included studies

Author	Type of study	Number of patients (Early/Non-early)	Country	Study period	Setting	Baseline time	Protocol details	Timing of NE initiation (min)	
								Early NE	Late NE
Elbouhy et al., 2019 [18]	RCT	101 (57/44)	Egypt	2017.01 -2018.12	Emergency room	Fluid infusion	Early: 30 mL/kg crystalloids, norepinephrine 5 μg/min via peripheral cannula Late: 30 mL/kg crystalloids, immediate ICU transfer, norepinephrine if MAP < 65 mmHg via central catheter	25 (20–30)	120 (120–180)
Permpikul et al., 2019 [17]	RCT	310 (155/155)	Thailand	2013.10 -2017.03	Emergency room	Fluid infusion	Early: Norepinephrine 0.05 μg/kg/min, IV fluids at discretion, vasopressors if MAP < 65 mmHg, 24 h Late: Placebo, IV fluids at discretion, vasopressors if MAP < 65 mmHg, 24 h	70 (50–90)	167 (125–273)
Ospina -Tascon et al., 2020 [19]	Prospective + PSM	186 (93/93)	Colombia	2015.01 -2017.02	ICU	Fluid infusion	Early: within 1 h. of admission or before first fluid bolus Late: after first fluid bolus based on clinical criteria	≤ 60	> 60
Xu et al., 2022 [9]	Retrospective + PSM	2862 (1431/1431)	USA	2008 -2019	ICU	Septic shock onset	Early: < 3 h. of septic shock Late: ≥ 3 h. of septic shock	< 180	≥ 180
Yeo et al., 2022 [10]	Retrospective + PSM	298 (149/149)	Korea	2019.09 -2020.02	Emergency room	Fluid infusion	Early: within 1 h. of first fluid bolus Late: after 1 h. of fluid bolus	≤ 60	> 60
Bai et al., 2014 [20]	Retrospective	213 (86/127)	China	2011.01 -2012.12	ICU	Septic shock onset	Early: < 2 h. after septic shock onset Late: ≥ 2 h. after onset	< 120	≥ 120
Colon Hidalgo et al., 2020 [21]	Retrospective	119 (76/43)	USA	2017.01 -2017.07	ICU	Septic shock onset	Early: within 6 h. of MAP < 65 mmHg Late: after 6 h. of MAP < 65 mmHg	< 360	≥ 360
Kang et al., 2020 [12]	Retrospective	80 (32/48)	China	2016 -2019	Emergency room and ICU	Fluid infusion	Early: < 3 h Late: after 3h	60	180
Jouffroy et al., 2022 [11]	Prospective	478 (143/335)	France	2016.04 -2020.12	Pre-hospital	Hospital admission	Early: Pre-hospital norepinephrine Late: No pre-hospital norepinephrine	Pre -hospital	Non pre-hospital
Li et al., 2024 [22]	Prospective	120 (42/78)	China	2021.09 -2022.06	ICU	Septic shock onset	Early: < 1 h Late: > 1 h	≤ 60	> 60

ICU, Intensive care unit; IV, intravenous; MAP, Mean arterial pressure; NE, Norepinephrine; PSM, propensity score matching; RCT, randomized controlled study

independently conducted these assessments. Disagreements were resolved by consulting a third author (CL). The certainty of evidence was assessed as high, moderate, low, or very low for the outcomes by using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) framework based on the assessment

of five domains: risk of bias, inconsistency, indirectness, imprecision, and other considerations (publication bias, large effect, plausible confounding, and dose response gradient) [15].

Statistical analysis

Meta-analysis was conducted to calculate odds ratios (OR) and confidence intervals (CI) using the Mantel–Haenszel statistical method. To assess statistical heterogeneity across studies, we applied Cochran's Q test and quantified it using I^2 statistic. An I^2 value of > 50% indicated substantial statistical heterogeneity. Given significant statistical and clinical heterogeneity, a random-effects model was used to pool the data. Forest plots were used to present the results of meta-analysis. Results from RCTs and studies using PSM method were pooled separately from results of cohort studies due to different types of study designs which may induce bias. Publication bias for outcome was assessed by visually inspecting funnel plots and conducting the Egger test [16]. All statistical analyses were performed using R software (version 4.3.1; R Foundation for Statistical Computing, Vienna, Austria). All tests were two-tailed, and statistical significance was set at $p < 0.05$.

Trial sequential analysis

To avoid increased risk of producing type I error in the meta-analysis by sparse data and repetitive testing of accumulating data, trial sequential analysis was applied to determine whether the evidence was reliable and conclusive. A cumulative Z-curve was constructed to evaluate the conclusiveness of the evidence. Conventional and trial sequential monitoring boundaries for the two timings of norepinephrine initiation groups were constructed. When the cumulative Z-curve crosses the trial sequential monitoring boundary or the futility area, the level of evidence for the intervention is sufficient and no further trials are needed. If Z-curve does not cross any of the boundaries, then the evidence is insufficient to reach a conclusion and further studies are warranted. In the current study, we calculated the required information size for trial sequential analysis using an α error of 0.05, a β error of 0.20, an anticipated OR reduction of 20% with early use of norepinephrine, and a control event proportion based our meta current study. In the analysis, the heterogeneity correction was set to variance-based, and a random-effects model was applied. All analyses were performed using trial sequential analysis version 0.9 beta (http://www.ctu.dk/tsa).

Results

Study selection

The process of study selection is presented in Fig. 1. Initially, we identified 2 751 records that were potentially eligible for inclusion after the removal of duplicates. After screening of titles and abstracts, 35 full-text articles were assessed for eligibility. Ultimately, we included ten studies, including two RCTs (411 patients) [17, 18], three PSM studies (3 346 patients) [9, 10, 19] and five observational studies (1 010 patients) [11, 12, 20–22] for a total of 4 767 patients. Two additional studies [23, 24] included in a recent meta-analysis [25] were incorporated into a secondary meta-analysis. These studies had been initially excluded due to the high proportion of patients not receiving vasopressors in the restrictive groups [23, 24].

Characteristics of the included studies

The characteristics of the included studies are shown in Table 1 and Table S1. The two RCTs were published in 2019 [17, 18]. The other observational studies were conducted from 2014 to 2023. The sample size ranged from 119 to 2 862 participants. Time to norepinephrine administration was measured from the start of fluid resuscitation in five studies [10, 12, 17–19] and from the onset of septic shock in four studies [9, 20–22]. Only one RCT [17] and two PSM studies [9, 19] reported mechanical ventilation-free days. Only two observational studies [20, 21] reported the cumulative norepinephrine dose.

Study quality assessments and publication bias

Among the two RCTs, one was assessed as having a low risk of bias [17], while the other raised some concerns regarding the overall risk of bias and the randomization process [18]. The five observational studies were categorized as having a medium quality risk of bias. Details of the risk of bias are provided in Additional file 2 and Supplementary figure S1.

Primary outcome: mortality

The analysis of the two RCTs showed that early initiation of norepinephrine was associated with a lower risk of mortality than a later initiation (OR 0.49, 95%CI: 0.25 to 0.96), with moderate heterogeneity ($I^2 = 45\%$, p = 0.04). When the analysis pooled the two RCTs and the three PSM studies (3 757 patients), the early start of norepinephrine was associated with a decreased mortality compared to a later start (OR: 0.65, 95%CI: 0.42 to 0.89) with high heterogeneity $I^2 = 74\%$, $p = 0.05$) (Fig. 2). The pooled estimate of five

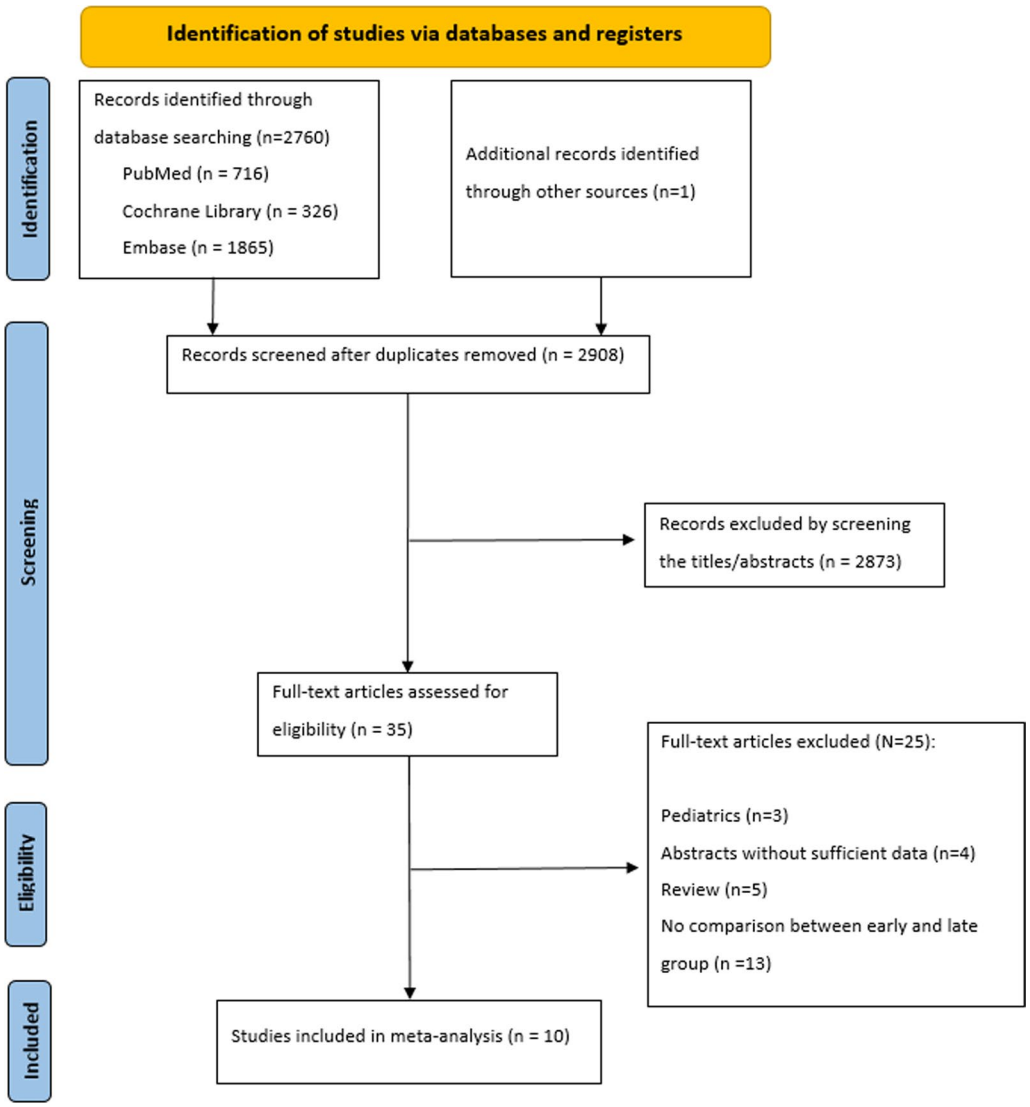
Identification of studies via databases and registers
Identification
Records identified through database searching (n=2760)
PubMed (n = 716)
Cochrane Library (n = 326)
Embase (n = 1865)
Additional records identified through other sources (n=1)
Screening
Records screened after duplicates removed (n = 2908)
Records excluded by screening the titles/abstracts (n = 2873)
Eligibility
Full-text articles assessed for eligibility (n = 35)
Full-text articles excluded (N=25):
Pediatrics (n=3)
Abstracts without sufficient data (n=4)
Review (n=5)
No comparison between early and late group (n =13)
Included
Studies included in meta-analysis (n = 10)

Fig. 1 Flowchart of literature selection

observational studies (1 010 patients) showed a similar result (OR = 0.71 (95%CI: 0.54 to 0.94), $I^2 = 66\%$, $p = 0.02$) (Fig. 2).

Trial sequential analysis for mortality showed that the cumulative Z-curve neither crossed the futility boundary nor reached the required information size, suggesting insufficient evidence and inconclusive result. A diversity-adjusted required information size of 8 251 patients was calculated. Thus, the current sample size including RCTs and PSM studies (3 757 patients) was below the required information size (Fig. 3).

Subgroup analysis and sensitivity analysis for mortality

The association between an early norepinephrine administration and lower mortality was observed in the subgroup with lactate level at baseline ≤ 3 mmol/L (OR 0.61, 95%CI: 0.43 to 0.86, $I^2 = 49\%$, $p = 0.006$) but not in the subgroup with baseline lactate > 3 mmol/L (Fig. 4).

A lower risk of mortality with early norepinephrine administration was observed if norepinephrine was started after 1 h (OR 0.70, 95%CI: 0.6 to 0.82, $I^2 = 74\%$) but not if norepinephrine administration started within 1 h (Fig. 4).

The sensitivity analysis, excluding one study at a time, was inconsistent with the primary analysis, except when excluding the study by Yeo et al. [10]. (Supplementary figure S2). The sensitivity analysis of observational studies, excluding the study by Bai et al., which involved patients who were severely hypotensive, did not demonstrate a favorable effect of early use of NE. The OR was 0.70

(95% CI: 0.36 to 1.36) with high heterogeneity ($I^2=74\%$, $p=0.29$) (Supplementary Figure S3. Additionally, when we excluded studies that used a definition of sepsis other than Sepsis 3, the analysis still did not show a beneficial effect of early NE use. For RCT and PSM studies, the OR was 0.75 (95% CI: 0.39 to 1.43), with high heterogeneity ($I^2=81\%$, $p=0.38$). For observational studies, the OR was 0.52 (95% CI: 0.26 to 1.03), with moderate heterogeneity ($I^2=50\%$, $p=0.13$) (Supplementary Figure S4).

Secondary outcomes

Time to achieve MAP target The pooled analysis of the two RCTs [17, 18] showed a significant reduction in time to achieve MAP target (mean difference: −1.30 h, 95%CI: −1.75 to −0.85; $I^2=0\%$, $p<0.05$) (Supplementary figure S5).

Fluid received during the first 6 h Analysis of RCTs and PSM studies demonstrated a significant reduction in the fluid volume received during the first 6 h in the group of early initiation of norepinephrine (mean difference = −502.63 mL, 95%CI: −899.23 to −106.03; $I^2=91\%$). No subgroup difference was found (Supplementary figure S6).

ICU length of stay Analysis of RCT and PSM studies showed no difference in ICULOS in the early norepinephrine initiation group compared to the other group (mean difference = −0.65 day, 95%CI: −2.47 to 1.17; $I^2=93\%$) (Supplementary figure S7). The pooled estimate of four observational studies showed no difference in ICULOS in the early norepinephrine initiation group compared to the other group (mean difference = 0.37 day, 95%CI: −1.42 to 2.15; $I^2=77\%$) (Supplementary figure S7).

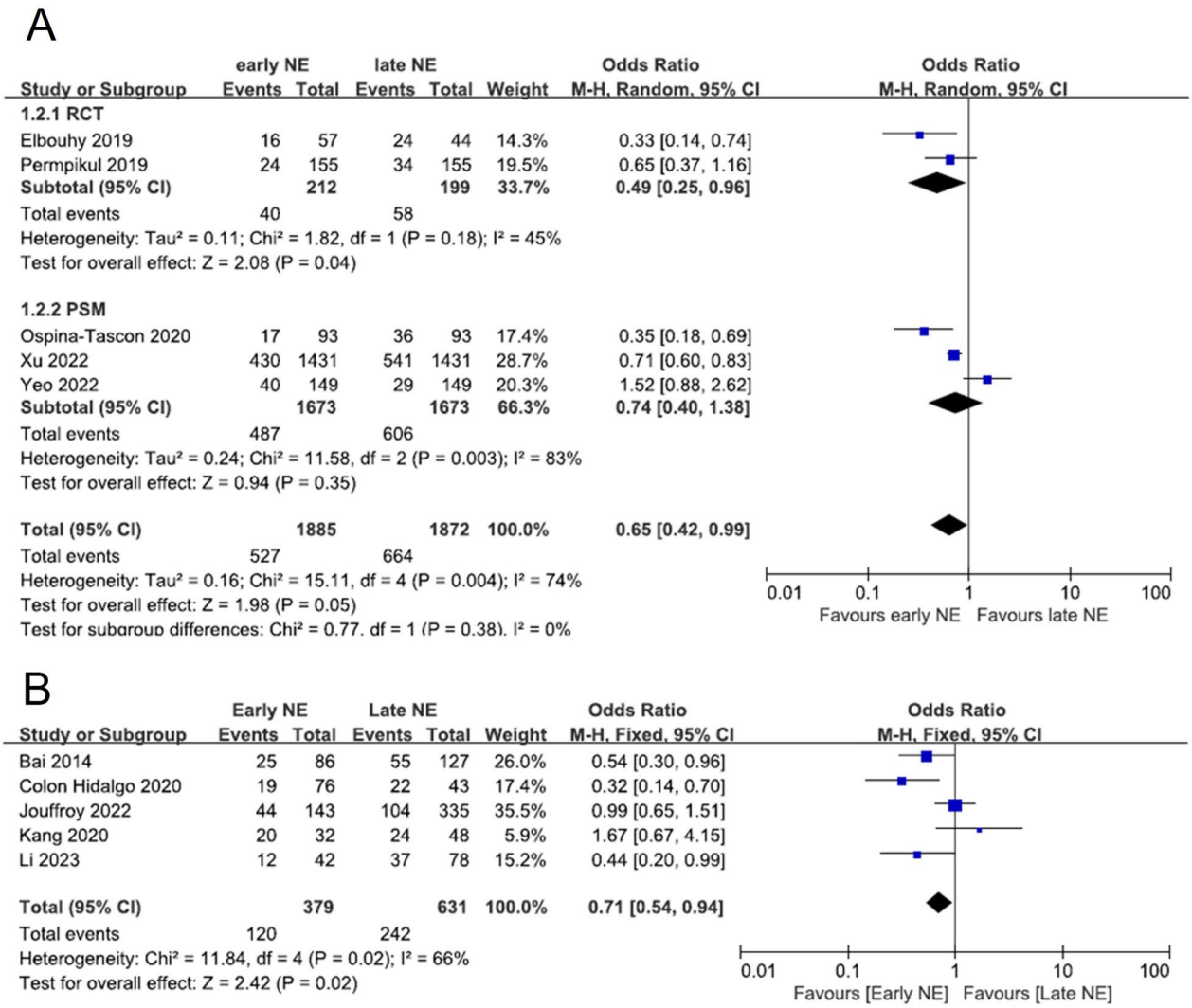
A
early NE
late NE
Odds Ratio
Odds Ratio
Study or Subgroup Events Total Events Total Weight M-H, Random, 95% CI
M-H, Random, 95% CI
1.2.1 RCT
Elbouhy 2019 16 57 24 44 14.3% 0.33 [0.14, 0.74]
Permpikul 2019 24 155 34 155 19.5% 0.65 [0.37, 1.16]
Subtotal (95% CI) 212 199 33.7% 0.49 [0.25, 0.96]
Total events 40 58
Heterogeneity: Tau² = 0.11; Chi² = 1.82, df = 1 (P = 0.18); I² = 45%
Test for overall effect: Z = 2.08 (P = 0.04)
1.2.2 PSM
Ospina-Tascon 2020 17 93 36 93 17.4% 0.35 [0.18, 0.69]
Xu 2022 430 1431 541 1431 28.7% 0.71 [0.60, 0.83]
Yeo 2022 40 149 29 149 20.3% 1.52 [0.88, 2.62]
Subtotal (95% CI) 1673 1673 66.3% 0.74 [0.40, 1.38]
Total events 487 606
Heterogeneity: Tau² = 0.24; Chi² = 11.58, df = 2 (P = 0.003); I² = 83%
Test for overall effect: Z = 0.94 (P = 0.35)
Total (95% CI) 1885 1872 100.0% 0.65 [0.42, 0.99]
Total events 527 664
Heterogeneity: Tau² = 0.16; Chi² = 15.11, df = 4 (P = 0.004); I² = 74%
Test for overall effect: Z = 1.98 (P = 0.05)
Test for subgroup differences: Chi² = 0.77, df = 1 (P = 0.38), I² = 0%
0.01 0.1 1 10 100
Favours early NE Favours late NE
B
Early NE
Late NE
Odds Ratio
Odds Ratio
Study or Subgroup Events Total Events Total Weight M-H, Fixed, 95% CI
M-H, Fixed, 95% CI
Bai 2014 25 86 55 127 26.0% 0.54 [0.30, 0.96]
Colon Hidalgo 2020 19 76 22 43 17.4% 0.32 [0.14, 0.70]
Jouffroy 2022 44 143 104 335 35.5% 0.99 [0.65, 1.51]
Kang 2020 20 32 24 48 5.9% 1.67 [0.67, 4.15]
Li 2023 12 42 37 78 15.2% 0.44 [0.20, 0.99]
Total (95% CI) 379 631 100.0% 0.71 [0.54, 0.94]
Total events 120 242
Heterogeneity: Chi² = 11.84, df = 4 (P = 0.02); I² = 66%
Test for overall effect: Z = 2.42 (P = 0.02)
0.01 0.1 1 10 100
Favours [Early NE] Favours [Late NE]

Fig. 2 Forest plot for mortality in (**A**) RCT and PSM studies, or in (**B**) observational studies. NE: Norepinephrine; PSM: propensity score matched; RCT: randomized control trial

Mechanical ventilation-free days at day-28 The pooled analysis of one RCT [17] and two PSM studies [9, 19] showed that the mechanical ventilation-free days was longer in the early norepinephrine initiation group (mean difference = 3.99 days, 95%CI: 2.42 to 5.57; $I^2 = 32\%$, $p < 0.05$) compared to the non-early norepinephrine initiation group (Supplementary figure S8).

Requirement of renal replacement therapy No significant association was observed between the requirement of renal replacement therapy and the early norepinephrine initiation in the RCT [17] and PSM [9, 10, 19] studies that investigated this association (OR 1.03, 95%CI: 0.87 to 1.22; $I^2 = 0\%$) (Supplementary figure S9).

Cumulative norepinephrine dose Analysis of two observational studies [20, 21] showed a decreased cumulative norepinephrine dose in the early norepinephrine initiation group (mean difference = −0.344 µg/kg/min, 95%CI: −1.426.13 to −0.76; $I^2 = 0\%$) (Supplementary figure S10).

Secondary analysis with two more RCTs For mortality and for each secondary outcome, pooled analysis included CLOVERS [24] and REFRESH [23] studies were consistent with primary analysis (Supplementary figures S11-S12)

Discussion

Our updated meta-analysis may suggest that early initiation of norepinephrine in patients with septic shock is associated with i) a significant reduction in mortality; ii) a decreased time to achieve the MAP target; iii) a reduction in fluid volume administered within the first 6 h of resuscitation and iv) an increase in mechanical ventilation-free days. Trial sequential analysis also suggests a trend toward statistical significance favoring early norepinephrine administration. However, this analysis is limited by the methodological weakness of the included studies and substantive confounding bias associated with the inclusion of PSM and observational trials. More data are needed to confirm these findings without risk of random error.

While there are arguments in favor of early administration of norepinephrine during septic shock, risks may be associated with this approach [26]. In the absence of clear data from large, well-conducted RCTs, the question of the time when norepinephrine should be started remains open. Some RCTs are underway to answer it (NCT05931601, NCT05836272, NCT04569942), but their results are pending. In this context, our results may be of interest.

Our main result was that early norepinephrine administration may reduce mortality compared with later administration. However, it must be emphasized that the

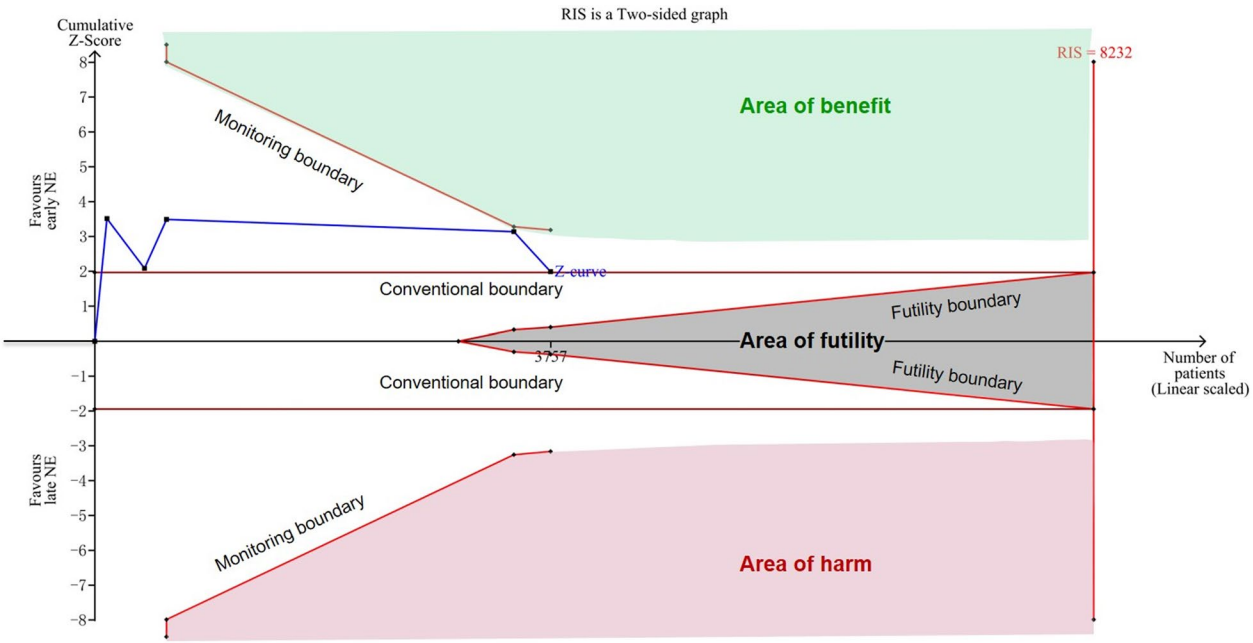

Fig. 3 Trial sequential analysis for mortality. The cumulative Z-curve neither crossed the futility boundary nor reached the required information size, suggesting insufficient evidence and inconclusive result. A diversity-adjusted required information size of 8 251 patients was calculated. NE: norepinephrine; RIS: required information size

trial sequential analysis showed insufficient evidence and an inconclusive result. Despite its limitations, subgroup analysis suggested that this strategy is also associated with a shorter time to reach a MAP target, a lower volume of fluid administered during the first 6 h, a shorter ICULOS, and more ventilator-free days. It also suggested that early norepinephrine may be more beneficial in patients with lactate level < 3 mmol/L and not administered within one hour. However, whether this effect was due to early norepinephrine administration per se and/or to the fact that patients were less severe remains an open question.

Our results are consistent with two earlier meta-analyses [8, 25]. Ahn et al. found no significant difference

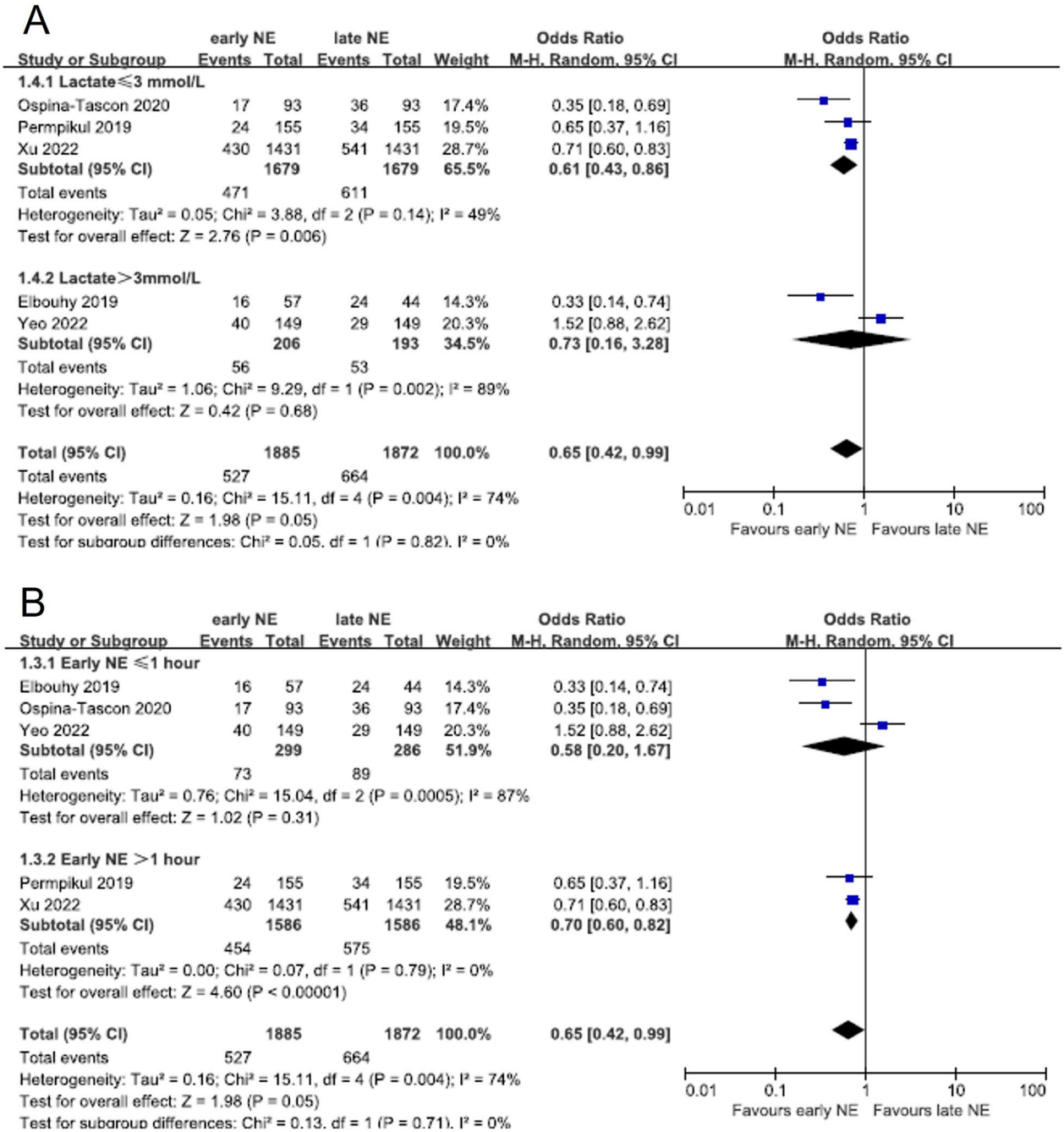
A
early NE
late NE
Odds Ratio
Odds Ratio
Study or Subgroup Events Total Events Total Weight M-H, Random, 95% CI
M-H, Random, 95% CI
1.4.1 Lactate≤3 mmol/L
Ospina-Tascon 2020 17 93 36 93 17.4% 0.35 [0.18, 0.69]
Permpikul 2019 24 155 34 155 19.5% 0.65 [0.37, 1.16]
Xu 2022 430 1431 541 1431 28.7% 0.71 [0.60, 0.83]
Subtotal (95% CI) 1679 1679 65.5% 0.61 [0.43, 0.86]
Total events 471 611
Heterogeneity: Tau² = 0.05; Chi² = 3.88, df = 2 (P = 0.14); I² = 49%
Test for overall effect: Z = 2.76 (P = 0.006)
1.4.2 Lactate>3mmol/L
Elbouhy 2019 16 57 24 44 14.3% 0.33 [0.14, 0.74]
Yeo 2022 40 149 29 149 20.3% 1.52 [0.88, 2.62]
Subtotal (95% CI) 206 193 34.5% 0.73 [0.16, 3.28]
Total events 56 53
Heterogeneity: Tau² = 1.06; Chi² = 9.29, df = 1 (P = 0.002); I² = 89%
Test for overall effect: Z = 0.42 (P = 0.68)
Total (95% CI) 1885 1872 100.0% 0.65 [0.42, 0.99]
Total events 527 664
Heterogeneity: Tau² = 0.16; Chi² = 15.11, df = 4 (P = 0.004); I² = 74%
Test for overall effect: Z = 1.98 (P = 0.05)
Test for subgroup differences: Chi² = 0.05, df = 1 (P = 0.82), I² = 0%
0.01 0.1 1 10 100
Favours early NE Favours late NE
B
early NE
late NE
Odds Ratio
Odds Ratio
Study or Subgroup Events Total Events Total Weight M-H, Random, 95% CI
M-H, Random, 95% CI
1.3.1 Early NE ≤1 hour
Elbouhy 2019 16 57 24 44 14.3% 0.33 [0.14, 0.74]
Ospina-Tascon 2020 17 93 36 93 17.4% 0.35 [0.18, 0.69]
Yeo 2022 40 149 29 149 20.3% 1.52 [0.88, 2.62]
Subtotal (95% CI) 299 286 51.9% 0.58 [0.20, 1.67]
Total events 73 89
Heterogeneity: Tau² = 0.76; Chi² = 15.04, df = 2 (P = 0.0005); I² = 87%
Test for overall effect: Z = 1.02 (P = 0.31)
1.3.2 Early NE >1 hour
Permpikul 2019 24 155 34 155 19.5% 0.65 [0.37, 1.16]
Xu 2022 430 1431 541 1431 28.7% 0.71 [0.60, 0.83]
Subtotal (95% CI) 1586 1586 48.1% 0.70 [0.60, 0.82]
Total events 454 575
Heterogeneity: Tau² = 0.00; Chi² = 0.07, df = 1 (P = 0.79); I² = 0%
Test for overall effect: Z = 4.60 (P < 0.00001)
Total (95% CI) 1885 1872 100.0% 0.65 [0.42, 0.99]
Total events 527 664
Heterogeneity: Tau² = 0.16; Chi² = 15.11, df = 4 (P = 0.004); I² = 74%
Test for overall effect: Z = 1.98 (P = 0.05)
Test for subgroup differences: Chi² = 0.13, df = 1 (P = 0.71), I² = 0%
0.01 0.1 1 10 100
Favours early NE Favours late NE

Fig. 4 Forest plot for mortality in different subgroups depending on (**A**) lactate level and (**B**) timing of initiation of norepinephrine. NE: Norepinephrine

in overall mortality but observed a significant reduction when studies with fluid-restrictive strategies were excluded [25]. Nevertheless, this analysis included the CLOVERS and REFRESH studies [23, 24], which we chose not to include in our primary analysis due to some methodological concerns. In the CLOVERS study, the median fluid volume administered before starting norepinephrine was 2 050 mL, i.e., approximately 28 mL/kg for a 70-kg adult. This may have induced significant fluid overload in the restrictive group, potentially confusing the comparison between early and delayed norepinephrine administration. Additionally, a substantial proportion of patients did not receive vasopressors even in the restrictive groups (52% and 41%, in CLOVERS and REFRESH studies, respectively). The outcomes may more reflect the comparison between liberal and restrictive fluid strategies than between early and later timings of norepinephrine initiation. These factors may explain the differences in mortality outcomes observed in their analyses [23, 24]. Nevertheless, including the REFRESH and CLOVERS studies in a post-hoc analysis aligned with our primary findings. Finally, the meta-analysis from Anh et al. included a study from Kusakabe et al. [27], which is a sub-analysis from the ARISE FLUIDS study [28]. It compared early with late vasopressor commencement in patients with sepsis and hypotension in the emergency department. However, different vasopressors were used, and only 63% of patients received norepinephrine [27].

While previous meta-analyses pooled raw data from observational studies, our analysis included, besides RCTs, only observational studies using PSM. Such PSM studies may be considered as quasi-experimental [29], which may have increased the robustness of our findings [30]. Also, the heterogeneity of studies, with variability in trial design, definition of septic shock and patient characteristics, was not considered in previous meta-analyses [8, 25]. To address this point, we performed several sensitivity analyses and found that the definitions of sepsis and septic shock, as well as the severity of hypotension, indeed affect the robustness of the final analysis. This highlights the importance of performing more homogeneous studies in the future to optimize the initiation of norepinephrine.

We also conducted subgroup analyses for mortality based on clinical perspectives, such as study design, timing of norepinephrine initiation, and baseline lactate levels. Additionally, we applied trial sequential analysis to assess the conclusiveness of the evidence, which suggested insufficient evidence and an inconclusive result for mortality, indicating the need for further high-quality RCT [12].

Our study has several limitations. First, the predominance of observational and PSM studies in our analysis may introduce bias and limit the generalizability of our findings. PSM only alleviates selection bias. Even though PSM attempts to balance covariates between groups, it cannot account for unmeasured confounders, which may affect the validity of the results. However, sensitivity analyses assessed the robustness of our findings by excluding studies with high risks of bias. Second, significant heterogeneity among studies may affect the robustness of our conclusions. Variations in study protocols, definitions of "early" administration, patient populations, and concomitant therapies contribute to this heterogeneity. This was also the case for criteria of septic shock diagnosis and for resuscitation protocols. Third, only few of the included studies evaluated secondary outcomes, limiting the analysis and interpretation of the latter. Fourth, included studies did not provide sufficient data on multiplicity and competing risks, which prevented us from performing a pooled analysis on these aspects. This may affect how our findings are interpreted. Future research should address this point for a more comprehensive understanding of the topic. Finally, the trial sequential analysis should not be overinterpreted, as PSM and observational studies were integrated despite their weaknesses and limitations. However, it still evaluated the conclusiveness of the evidence, and suggested the necessity of further RCTs.

Conclusion

In conclusion, early initiation of norepinephrine may improve some clinical outcomes in septic shock without increasing adverse events. These results may suggest that this attitude is reasonable. Nevertheless, high-quality, adequately powered RCTs are still needed to confirm the relevance of this strategy, and to better define which patients with septic shock may benefit from it.

Abbreviations

CI	Confidence interval
ICU	Intensive care unit
LOS	Length of stay
MAP	Mean arterial pressure
OR	Odds ratio
PSM	Propensity score matching
RCT	Randomized controlled trial

Supplementary Information

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Supplementary file 1

Author Contribution

R.B., X.M. and C.L. designed the work; R.B., M.D., A.S., V.A. made the acquisition; R.S, R.B., W.G. made the analysis; R.S, R.B., X.M., W.G., V.A. and C.L. interpreted the data; R.S. and R.B. have drafted the work; X.M., G.O., C.P. and C.L.substantively revised it; All authors reviewed the final manuscript.

Availability of data and materials

No datasets were generated or analysed during the current study.

Declarations

Human ethics and consent to participate declarations
Not applicable.

Competing interests
X.M. is a member of the Medical Advisory Board of Pulsion Medical Systems (Getinge) and received honoraria for lectures from Pulsion Medical Systems (Getinge), Baxter and AOP health. The authors declare no competing interests.

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